

**UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA**

**DOCTORAL SCHOOL**

**PhD Thesis**

**ABSTRACT**

**CLINICAL, ETIOLOGIC AND IMAGING EVALUATION OF THE**

**ENTHESEAL INVOLVEMENT IN REACTIVE ARTHRITIS**

**PATIENTS**

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## **Chapter I**

### **Definition, History, Terminology, Classification criteria, Epidemiology Reactive Arthritis**

Reactive arthritis is an inflammatory joint disease which develops after 1-4 weeks following an enteral, genital or ORL infection, with a higher frequency in HLA-B27 positive patients. A characteristic that differentiates it from an infectious arthritis is the fact that in the synovial fluid was not found pathogen microorganisms.

Reactive arthritis is part of the seronegative spondyloarthropathy group along with: ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, undifferentiated spondyloarthropathy and non-radiological spondyloarthropathy. The characteristics of this group are:

- Peripheral, asymmetrical arthritis, predominantly affecting the lower limbs
- Absence of the subcutaneous nodules specific to the rheumatoid arthritis
- Extraarticular features such as acute anterior uveitis, pulmonary fibrosis of the superior lobes
- Enthesitis, the inflammatory affection of entheses
- The constant absence of the rheumatoid factor
- Genetic predisposition
- Presence of HLA-B27 antigen

From an epidemiological point of view, reactive arthritis can be found at patients of any age, with a higher frequency at young people aged 20 to 40 years. On the other hand, there are no differences between men and women, an important role being played by HLA-B27.

## **Chapter II**

### **Etiopathogeny**

#### **Genetic factors represented by HLA-B27 molecule**

HLA-B27 represents the genetic characteristic of the seronegative spondyloarthropathy group, being found in 90% of the ankylosing spondylitis cases and in the 60-70% of reactive arthritis cases. The presence of this antigen is associated with a severe evolution of arthritis, frequent extraarticular features and an unfavorable prognostic disease. But, according to a population study, at patients with a negative HLA-B27 antigen, the disease has a milder evolution, rare extraarticular features and a better evolution on a long term versus patients with HLA-B27 present.

#### **Infectious agents associated with reactive arthritis**

The mucous membrane of the urogenital or gastrointestinal tract represents the most frequent place through which infection penetrates the organism. Chlamydia trachomatis and Ureaplasma urealyticum are considered the determinant agents of the genital infection, being more frequently encountered than Mycoplasma genitalium. A pathogen respiratory agent, such as Chlamydia pneumoniae, is found in approximately 10% of patients with reactive arthritis.

When it comes to gastrointestinal tract, the most frequent infectious agents associated with reactive arthritis are: Yersinia, Salmonella, Shigella and Campylobacter. In the past, Shigella flexneri was considered the only species of Shigella connected to reactive arthritis, but an epidemiological study from Finland demonstrated that Shigella sonnei and Shigella dysenteriae can also be involved in the pathogenesis of this disease.

### **Chapter III**

#### **The diagnosis of reactive arthritis**

##### **III.1. The clinical diagnosis**

###### **III.1.1. The articular syndrome**

The main clinical expression of the arthritis is represented by the asymmetrical oligoarthritis, being present predominantly at the lower limbs. The joints most affected in this disease are the knees and the ankles.

When it comes to axial affection, the disease is characterized by an inflammatory pain at the lumbar spine, which irradiates down the sacrum translating the presence of sacroiliitis, having an unilateral and asymmetrical debut. In time it becomes symmetrical and bilateral.

Dactylitis is one of the characteristics of the negative spondylarthritides group, being translated as an inflammation at the proximal interphalangeal and metacarpophalangeal joints along with flexor tenosynovitis. It is more commonly encountered in the cases with Chlamydia trachomatis.

###### **III.1.2. Extraarticular features**

###### **Mucocutaneous involvement**

Keratoderma blennorrhagica appears at 15% of the patients. It is observed late in the course of the disease, at 4-6 weeks after the onset of the urethritis. When the lesions occur at the scalp and the body, it is mimicking from a macroscopically point of view a pustular psoriasis. Initially, there are papules or vesicles which confluence and forms hyperkeratosis lesions at the hands and feet.

The circinate balanitis is the most frequent mucocutaneous lesion found in reactive arthritis. The small erythematous papules and pustules unite and form erosive crusting at the

gland of the penis. At uncircumcised men, the aspect is of erosion and not a crust, due to the fact that moisture and trauma slow down the forming of the crust.

Oral ulcers are often unpainful and can pass without notice by the patients.

### **Gastrointestinal involvement**

Reactive arthritis due to a gastrointestinal infection with *Yersinia enterocolitica*, *Salmonella* or *Shigella*, manifests clinically by an accelerated bowel movement, abdominal pain and rarely dehydration.

### **Genitourinary involvement**

Reactive arthritis due to urogenital infection with *Chlamydia trachomatis* and *Ureaplasma urealyticum* manifests through urethritis. It can also be associated with prostatitis, orchepididimitis, and hemorrhagic cystitis. The disease manifests severely in men.

### **III.1.3. Other features**

#### **Ocular involvement**

Conjunctivitis represents the inflammation of the transparent membrane (known as conjunctive) which is lining the eyelids all the way to the corneal edge. Usually it appears in infections with *Shigella*, *Salmonella* and *Campylobacter jejuni*, rarely being found in cases with *Yersinia*. Evolution is limited at approximately 5-7 days, but the complicated cases can prolong for 6 months.

#### **Cardiac involvement**

In reactive arthritis it can be found the following: cardiac conduction disorders and atrioventricular blocks of first degree. The incidence is approximately 10% of patients with severe forms. Also, it can be encountered aortic insufficiency.

#### **Renal involvement**

The renal manifestation is glomerular nephropathy with deposits of IgA and renal amyloidosis, which is sporadic.

### **III.2. Imagistic diagnostic**

#### **III.2.1. Conventional radiography**

The radiological exploration is the most used technique in the medical imaging world. It can identify bone productions in the tendinous areas (calcaneus, trochanter, tibial tuberosity), tendinous calcifications, tendinous ossifications, sacroiliitis, asymmetrical syndesmophytes with a rough aspect at the dorsal and superior lumbar spine. Furthermore, it

can make the differential diagnosis with rheumatoid arthritis, when it comes to peripheral affection by demonstrating the lack of erosions and pinching joint specific to rheumatoid arthritis.

### **III.2.2. Nuclear magnetic resonance**

Nuclear magnetic resonance (MRI) is the only imaging method available which can present directly the bony, cartilaginous and soft tissue components of the joint simultaneously. Therefore, MRI has the capacity of demonstrating not only the inflammatory synovitis with or without contrast, but also the bony erosions before they appear on a conventional radiography.

### **III.2.3. Ultrasonography**

Ultrasonography represents an imaging method that uses ultrasounds reflected on the human body as a vector of the medical information. One of the advantages of using it is the fact that ultrasounds are harmless for the human body. Ultrasonography (US) is the only method of examination in real time which allows the doctor to appreciate the pathological modifications at an articular level but also at tendons and entheses. Ultrasonographically speaking, enthesitis is defined by: loss of normal fibrillar echostructure of the tendons at the joints, inhomogeneous structure, and irregularity of the edges and the thickening of them. The tendons will be measured by using the transducer in longitudinal position. The disadvantages of US start from the fact that is operator dependent.

## **Chapter IV: Objectives**

The study proposes a complete evaluation of the pathogenesis process and clinical features with the help of the classical investigation methods as well as with modern imaging techniques.

Main objectives of the study were:

1. Identifying the types of enthesal involvement in reactive arthritis (ReA) patients, compared to other spondylarthritides and degenerative diseases.
2. To compare main clinical and biological features of the patients in the first group, depending on the infection etiology.
3. To identify a clinical and imaging profile of the enthesal involvement, depending on the infection etiology.

***Secondary objectives:***

1. To identify evolutive features and the meaning of enthesitis, of the HLA-B27 antigen and inflammation markers, in patients with ReA, from the first group.

2. To establish some correlation between the enthesal involvement and radiologic and MRI changes, in lumbar spine and sacroiliac joints.

## **Chapter V: Material and method**

The study took place in the Rheumatology Clinic Of UMF Craiova in a period between January 2012 and December 2015, being a transversal study. The total number of patients included 112, separated in three batches:

- The first batch formed by 52 patients with reactive arthritis;
- The second batch formed by 30 patients suspected of other negative spondyloarthropathy;
- The third batch formed by 40 patients with osteoarthritis.

The tools used in achieving these objectives were:

- In the Rheumatology Clinic of UMF Craiova, for the musculoskeletal ultrasound (US) evaluation, it was used an Esaote MyLab 25 ultrasound machine, with a high frequency transductor(10-18MHz)
- In the Department of Radiology there were used: Precision Rxi digital camera with 2 stations, Soft Windows XP, with digital working of images and printer on the thermal film; MRI 3Tesla System which presents a super conductible magnet long-shot(162cm), diameter gantry 70cm, unlimited number of channels and FOV maxim 55 cm. The MRI system used allowed the rapid parallel acquisition of the images, as well as full body scanning. The Body Pro package allowed high resolution scanning, having functions 2D and 3D, THRIVE compatible with the sequences with fat suppressed and PROSET with volume acquisition 3D in T1 sequences.

For the determination of the infectious trigger it has been used the following:

- Cultures from the urethral or vaginal secretions, urocultures with the purpose of detecting the presence of Chlamydia Trachomatis
- Serological testing in dynamic of the antibodies against specific bacteria: Chlamydia, Yersinia, Campylobacter
- Stool exam for identification of infections with Salmonella, Shigella

The immunological and biological investigations were conducted in the Laboratory of County Clinical Hospital Craiova and in the Immunology Department of University of Medicine and Pharmacy Craiova. For the detection of Chlamydia, it was used direct immunofluorescence technique, which consisted in detecting antigens and antibodies in one step, when the serum marked with fluorescent antibodies was added to the microscopic sample.

For the detection of HLA-B27 antigen through lympho-toxicity test, were used microtiter plates with anti HLA-B27 serum, applied to wells.

Data collection was performed for each patient, including clinical data from admitting to hospital, clinical evolution and laboratory investigations according to the protocol from the beginning of the study.

Every patient signed the informed consent about the use of personal data and performing biological and imaging explorations.

Data were processed using Cross, Basic Tables, correlate, regression, Factor Analysis and Data Analysis commands from Excel and XLStat 2014 module (graphics, charts, statistical tests).

## **CONCLUSIONS**

- Sacroileitis represents a feature to confirm the spondylarthritides diagnosis. Identifying it and treating it early, could limit the progressive cases to chronic disease.

- The presence of enthesitis can suggest the spondylarthritides diagnosis and offers the possibility of an optimal, targeted management, with permanent imaging monitoring.

- Ultrasonography represents a non invasive method, accessible, which can be performed at patient's presentation. This technique allowed identification of asymptomatic enthesitis, suggesting subclinical involvement.

- Patients with enthesal involvement tend to have a more aggressive disease, frequently with a chronic progression. In the same time, our study confirmed data from literature, related to a frequent association between high disease activity and enthesal involvement.

- Chlamydia trachomatis is the most frequent trigger for reactive arthritis. Some specific feature in our study was that most of the patients were women aged between 20-29 years old from urban areas.

- the presence of HLA-B27 antigen is associated with both increased joint destruction, as erosions and sacroiliitis and multiple extraarticular features.